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Topic 11 – Proliferation, apoptosis, microparticles

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0243

Effect of diabetes on cardiac microparticles release following coronary artery ligation

Min Yin (1), Kiave-Yune Howangyin (2), Xavier Loyer (1), Jean-Sébastien Silvestre (2), Chantal Boulanger (1)
(1) Inserm U970, Equipe 1, Paris, France – (2) Inserm U970, Equipe 6, Paris, France

Background: Microparticles (MPs) are 0.1-1 μm membrane-shed vesicles released following cell activation/apoptosis. Little is known about how MPs release in the ischemic myocardium. We aimed to evaluate the cardiac MPs release after myocardial infarction (MI) in diabetic mice.

Methods: C57BL/6 mice were treated by streptozotocin and coronary artery ligation was performed during 6 hours to 72 hours at the end of 12 weeks' hyperglycemia. MPs from both sham and ischemic myocardial muscles obtained from control and diabetic mice were isolated after sequential centrifugation. Flow cytometry analysis quantified the peak formation of phosphatidylserine+MPs (PS+MPs) using annexin V. Plasma MPs were also analyzed and compared to those observed in cardiac tissues. A GFP-α-actin transgenic mouse model was used to characterize the GFP packing in cardiac MPs.

Results: PS-rich MPs were measurable in the mouse heart. In control mice, cardiac MP level increased till 15 hours after ligation, then returned to a basal level 72 hours later. In diabetic mice, myocardial MP increase following MI was delayed and more transient than in control mice after onset of coronary arteries ligation. Cardiac MP levels showed no significant difference between diabetic mice and control mice. Cardiac MPs were also isolated from GFP-α-actin transgenic mice heart. 39% PS+MPs showed GFP+, demonstrating that they were originating from cardiomyocytes. The platelet-free plasma of control mice contained extremely low levels of PS+MPs. Plasma MP levels were higher in diabetic mice than in control mice.

Conclusion: This study reports for the first time that coronary artery ligation transiently increases local MPs generation in mouse heart, in particular those originating from cardiomyocytes. MPs levels were increased in both plasma and heart of diabetic mice, where they could contribute to disease progression.

0254

Soluble adenylyl cyclase regulates cardiac mitochondrial membrane permeabilization under calcium stress

Zhenyu Wang (1), Claire Nicolas (1), Delphine Courilleau (2), Gregoire Vandecasteele (1), Rodolphe Fischmeister (1), Catherine Brenner (1)
(1)Inserm U 769, Châtenay-Malabry, France – (2) IFR141-Ciblot, Châtenay-Malabry, France

cAMP is an important messenger of neurohormonal regulation of the heart. cAMP regulates many cellular functions such as gene expression, excitation-contraction coupling and cellular metabolism. cAMP is produced by adenylyl cyclases (AC) and degraded by phosphodiesterases (PDEs). Most AC isoforms are membrane proteins except a bicarbonate (HCO_3^-)-regulated soluble isoform (sAC). The existence and role of a sAC/cAMP signaling in mitochondria has been postulated in various tissues including liver (1), brain (2) and neonatal cardiomyocytes (3), but has not been demonstrated in adult cardiomyocytes. The goal of this study was to demonstrate the existence of a mitochondrial cAMP-signalling pathway and explore its influence on mitochondrial function and cell fate. To that end, cardiac mitochondria were isolated as a homogenous, pure and functional suspension from adult rat and mouse heart. sAC, exchange proteins directly activated by cAMP (Epac1 and 2) and PDEs were co-detected with constitutive proteins such as ANT and VDAC in mitochondria. At low respiratory substrate concentration, HCO_3^- activated sAC-dependent cAMP production and hyperpolarized the mitochondrial membrane independently of pH. At high respiratory substrate concentration, HCO_3^- maintained the membrane potential and delayed matrix swelling and cytochrome *c* release under Ca^{2+} stress. Moreover, cAMP production stimulated mitochondrial oxygen consumption. The implication of PDEs, Epac and PKA is currently under investigation using pharmacological modulators. In conclusion, sAC can regulate mitochondrial membrane permeabilization and stimulate mitochondrial respiration in adult cardiomyocytes. This might constitute a novel cardioprotective mechanism through preservation of mitochondrial function in pathophysiological conditions of calcium overload.

0250

Circulating microparticles from obstuctive sleep apnea syndrome patients induce endothelin-mediated angiogenesis

Simon Tual-Chalot (1), Frédéric Gagnadoux (2), Wojciech Trzepizur (2), Pascaline Priou (2), Ramaroson Andriantsitohaina (1), Maria Carmen Martinez (1)
(1) Inserm 1063, Faculté de Médecine, Angers, France – (2) CHU d'Angers, Pneumologie, Angers, France

Microparticles are deemed true biomarkers and vectors of biological information between cells. Depending on their origin, the composition of microparticles varies and the subsequent message transported by them, such as proteins, mRNA, or miRNA, can differ. In obstructive sleep apnea syndrome (OSAS), circulating microparticles are associated with endothelial dysfunction by reducing endothelial-derived nitric oxide production. Here, we have analyzed the potential role of circulating microparticles from OSAS patients on the regulation of angiogenesis and the involved pathway. For this, microparticles from twenty OSA patients and fifteen non-OSA subjects were used. Both VEGF plasma levels and content carried by circulating microparticles from OSAS patients were increased when compared with microparticles from non-OSAS patients. Neither microparticles from OSAS or non-OSAS patients affect endothelial cell apoptosis and migration. However, microparticles from OSA patients but not from those non-OSA subjects enhanced endothelial cell proliferation. Circulating microparticles from OSAS patients induced an increase of angiogenesis in human aortic endothelial cells that was abolished in the presence of the antagonist of endothelin-1 receptor type B. In addition, endothelin-1 secretion was increased in human endothelial cells treated by OSAS microparticles. We highlight that circulating microparticles from OSAS patients can modify the secretome of endothelial cells leading to angiogenesis.

0424

Early increase in total O-GlcNAc can be protective during sepsis

Valentine Prat (1), Marine Ferron (1), David Roul (1), Virginie Aillerie (1), Angélique Erraud (1), Amandine Grabherr (1), John Chatham (2), Benjamin Lauzier (1), Bertrand Rozec (3), Chantal Gauthier (1)
(1) Inserm UMR 108, Institut du Thorax, Nantes, France – (2) University of Alabama, Division of Molecular and Cellular Pathology, Pathology, Birmingham, Etats-Unis – (3) Nantes-Laennec Hospital, Anaesthesiology and intensive care unit, Nantes, France

Each year, 750 000 cases of septic shock occurs in the US. Nöt et al. (2010) showed that O-GlcNAc stimulation, the final product of hexosamine biosynthetic pathway (HBP), could improve patient outcome in haemorrhagic shock. We postulated that early stimulation of the HBP in septic shock could be of interest to improve patient survival. So we investigated two different ways of O-GlcNAc stimulation: by increasing its activation by addition of glucosamine (GLCN), or by inhibiting O-GlcNAcylation degradation by an inhibitor of O-GlcNAcase (NbutGT).

Twelve weeks-old SD rats received either lipopolysaccharide (LPS, 5 mg/kg) or saline intravenously (IV). One hour later, fluid resuscitation (15 mL/kg of colloid) was associated or not with GLCN (270 mg/kg) or NbutGT (50 mg/kg). Blood pressure was recorded during all the protocol. Three hours later, heart and blood samples were collected to evaluate HBP by western blot (global protein

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